PATENT
Attorney Docket No. 06267.0126-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
Tomi JÄRVINEN et al.	) Group Art Unit: 1626
Application No.: 10/537,622	) Examiner: Laura L. STOCKTON
Int'l Filing Date: December 5, 2003 § 371 Date March 29, 2006	)
For: IMIDAZOLE DERIVATIVES HAVING AFFINITY FOR ALPHA 2 RECEPTORS ACTIVITY	) Confirmation No.: 8385

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER BOARD RULE § 41.37

In support of the Notice of Appeal filed concurrently herewith, and further to Board Rule 41.37, Appellants present this brief and enclose herewith the fee of $540.00 required under 37 C.F.R. § 1.17(c).

This Appeal Brief is being filed concurrently with a petition for an Extension of Time for three (3) months, and the appropriate fee.

This Appeal responds to the June 11, 2008, final rejection of claims 1-10.

If any additional fees are required or if the enclosed payment is insufficient, Appellants request that the required fees be charged to Deposit Account No. 06-0916.

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Real Party In Interest

Orion Corporation is the real party in interest indicated by the assignment recorded on March 29, 2006 at Reel 017380, Frame 0669.

Related Appeals and Interferences

There are currently no other appeals or interferences, of which appellants, appellants' legal representatives, or Orion Corporation are aware, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Status Of Claims

Claims 1-10 are pending. Claims 1-10 are finally rejected. *See* June 11, 2008 Final Office Action ("Final Office Action").

Specifically, in the Final Office Action, pages 2-9, claims 1-10 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over WO 97/12874 to Karjalainen et al. ("*Karjalainen*") taken alone or in view of WO 01/51472 to Huhtala et al. ("*Huhtala*").

Claims 11-12 have been canceled.

Claims 1-10 are under appeal.

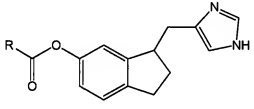
Status Of Amendments

Appellants' claim amendments to claims 1, 4, and 7-10 and cancellation of claims 2-3 and 5-6 submitted pursuant to 37 C.F.R. § 1.116 on October 10, 2008, were "not deemed to place the application in a better form for appeal . . . ." *See* October 28, 2008, Advisory Action. As a result, the Office indicated that for the purposes of appeal, the amendments would not be entered. *See id.*

Summary Of Claimed Subject Matter

The present claims recite compounds useful as bioreversible pro-drugs of MPV-2426, an alpha$_2$-adrenergic agonist. *See* Specification at page 1, Field of the Invention. The presently claimed compounds are chemically stable in non-enzyme medium, have suitable lipophilicity, i.e., they are able to permeate through biological membranes, and they are readily hydrolyzed to the parent drug *in vivo*. *See* Specification at page 2, lines 1-4.

One embodiment of the present invention, as recited in **independent claim 1**, is a compound of general formula I,



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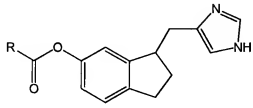
or a pharmaceutically acceptable salt or hydrate thereof, wherein R represents unsubstituted or substituted lower alkyl, unsubstituted or substituted aryl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted lower alkylamino or a saturated five or six membered heterocyclic group containing one or two nitrogen atoms.

One embodiment of the present invention, as recited in **dependent claim 7**, is a method for the treatment of hypertension, glaucoma, migraine, diarrhea, ischemia, addiction to a chemical substance, hypotension, shock, cardiopulmonary resuscitation, a withdrawal syndrome, congestive heart failure, anxiety, or for achieving sedation or analgesia, or for reducing nasal congestion, or for achieving anesthesia with an adjunct,

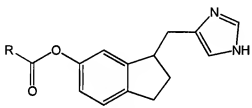
which comprises administering to a mammal in need thereof an effective amount of a compound of formula I,



(I)

or a pharmaceutically acceptable salt or hydrate thereof, wherein R represents unsubstituted or substituted lower alkyl, unsubstituted or substituted aryl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted lower alkylamino or a saturated five or six membered heterocyclic group containing one or two nitrogen atoms.

One embodiment of the present invention, as recited in **dependent claim 9**, is a pharmaceutical composition which comprises as an active agent a compound of formula I,



(I)

or a pharmaceutically acceptable salt or hydrate thereof, wherein R represents unsubstituted or substituted lower alkyl, unsubstituted or substituted aryl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted lower alkylamino or a saturated five or six membered heterocyclic group containing one or two nitrogen atoms, and optionally a pharmaceutically acceptable excipient.

Grounds of Rejection

One ground of rejection is to be reviewed in this appeal:

(1) the rejection of claims 1-10 under 35 U.S.C. § 103(a) as being obvious over *Karjalainen* either alone or in view of *Huhtala*.

Argument

I. Rejection of Claims 1-10 under 35 U.S.C. § 103(a)

The Office rejected claims 1-10 under 35 U.S.C. § 103(a) as allegedly being unpatentable over *Karjalainen* either alone or in view of *Huhtala*. June 11, 2008, Final Office Action ("Final Office Action") at 3. Appellants respectfully traverse this rejection and assert that the Office has failed to establish a *prima facie* case of obviousness.

As a threshold issue, Appellants respectfully point out that the nomenclature of the specific esters (e.g., RC(O)OR) disclosed in both *Karjalainen* (page 4, lines 27-28) and *Huhtala* (page 8, third paragraph, last sentence), namely, methyl, ethyl, and propyl esters, is inconsistent with standard IUPAC nomenclature of esters. For example, a generic methyl ester is depicted by the following formula, where the arrow is pointing to the methyl group:

As can be seen from that example, a "methyl ester" connotes that the methyl group is attached to the oxygen (O) of the ester. By analogy, an "ethyl ester" would have an ethyl group connected via the oxygen of the ester.

In contrast, the potential esters formed from the *Karjalainen* and *Huhtala* compounds cannot be called methyl, ethyl, or propyl esters according to standard IUPAC nomenclature are impossible. For example, *Karjalainen* teaches that when one of R_4 to R_8 is a hydroxy group, esters can be formed. *Karjalainen* at 4, lines 25-26; *see also Huhtala* at 8, third paragraph. This necessarily means that the compound itself in

Karjalainen (see Figure 1.) (and *Huhtala* (see Figure 2.)) is connected to the oxygen of the ester, i.e., the hydroxy group (R_4 to R_8) is derivatized to become an ester:

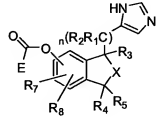


Figure 1. Generic compound of *Karjalainen*, where R_6 forms an ester.

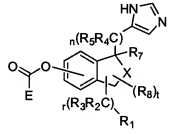


Figure 2. Generic compound of *Huhtala*, where R_6 forms an ester.

While esters of the *Karjalainen* and *Huhtala* compounds are certainly chemically possible, those esters cannot be correctly named methyl, ester, or propyl esters.

Appellants recognize that both *Karjalainen* and *Huhtala* could be referring to esters where the E group in the example above is a methyl, ethyl, or propyl group. However, as Appellants note, those compounds would not be correctly named as methyl, ethyl, or propyl esters, respectively. As a result of this ambiguity in nomenclature, Appellants assert that the Office can rely on *Karjalainen* and *Huhtala* for only their broad teaching that the hydroxy groups of their respective compounds can be derivatized as esters, and not for any specific teaching of what esters may result. However, for the sake of a fully developed brief, Appellants also argue their case as though *Karjalainen* and *Huhtala* could be (incorrectly) interpreted to teach compounds where E is methyl, ethyl, or propyl.

Rejection over Karjalainen Alone

To support its rejection, the Office states that "the difference between the compounds of the prior art and the compounds instantly claimed is that the instant claims compounds are generically described in the prior art." Final Office Action at 3.

The Office appears to be using an obvious-to-try standard to establish its case with respect to *Karjalainen*. However, Appellants respectfully point out that such a standard can be used only when there are a "finite number of identified, predictable solutions, with a reasonable expectation of success." M.P.E.P. § 2141. In the present case, *Karjalainen* does not teach a finite number of identified, predictable solutions. Instead, the esters generally contemplated by *Karjalainen* include at least thousands of possible compounds. As a consequence, one of ordinary skill in the art would not be likely to "at once envisage" the presently claimed genus of esters as required under *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962); *see also* M.P.E.P. § 2144.08.

Even if the Board disagrees with Appellants and considers *Karjalainen* for its specific teaching where E above could be methyl, ethyl, or propyl, the three esters that result do not render obvious the invention as presently claimed as a whole. In particular, *Karjalainen* provides no reason to one of ordinary skill in the art to modify those three specific esters of *Karjalainen* to arrive at, for example, the compounds where R in the present claims is an aryl group or an "unsubstituted or substituted heteroaryl, unsubstituted or substituted lower alkylamino or a saturated five or six membered heterocyclic group containing one or two nitrogen atoms."

The Office (or the prior art) must delineate a reason for such modification even after the Supreme Court's *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007)

decision. In particular, the Federal Circuit held that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chem. Ind., Ltd. v. Alphapharm PTY., Ltd.* 492 F.3d 1350, 1357 (Fed. Cir. 2007). Neither the broad nor specific teachings of *Karjalainen* provides a reason to modify its compounds in a "particular manner" to arrive at the presently pending claims. Indeed, none of the specific compounds disclosed in *Karjalainen* includes **any** ester functionality. *See Karjalainen* at 13-39. Therefore, not only does *Karjalainen* fail to provide a finite number of predictable solutions, in general, it likewise contains no specific example of any compounds possessing an ester functional group. Consequently, the Office has failed to establish a *prima facie* case of obviousness over *Karjalainen*, and this rejection should be withdrawn.

Rejection over Karjalainen in View of Huhtala

Appellants further assert that the Office has failed to establish a *prima facie* case of obviousness over *Karjalainen* in view of *Huhtala* for the reasons stated above, and for the additional reason that *Huhtala* teaches away from its combination with *Karjalainen*.

The presently pending claims are non-obvious over *Karjalainen* in view of *Huhtala* because *Huhtala* fails to compensate for *Karjalainen's* deficiencies, namely a specific teaching that would lead one of ordinary skill in the art to modify the compounds of *Karjalainen* to arrive at compounds falling within the scope of the presently pending claims. Even though *Huhtala* contemplates ester functional groups on the benzene ring (page 8, third full paragraph), its disclosure is no more helpful than *Karjalainen's*, and, in

fact, includes the same nomenclature ambiguity discussed above. Indeed, *Huhtala* discloses the same specific "esters" that *Karjalainen* teaches: methyl, ethyl, and propyl. Compare *Karjalainen* at 4, lines 27-28 with *Huhtala* at 8, last sentence of third paragraph.

The Office relies on *Huhtala* "to show the various types of esters formed from the hydroxy groups." Final Office Action at 9. Because that reliance fails to augment what *Karjalainen* already teaches, *Karjalainen* in view of *Huhtala* cannot render obvious the present claims for the reasons presented above.

Importantly, the disclosure of *Huhtala* actually teaches away from the presently claimed esters. In particular, *Huhtala* teaches that its compounds may be derivatized as esters, but that those esters "retain the pharmacological properties of the free form [i.e., drug molecule]." *Huhtala* at 8. In contrast, the pro-drugs, i.e., esters, of the present claims are "pharmacologically inactive derivatives of drug molecules." Specification at page 1, Background of the Invention, third para. Therefore, the disclosure of *Huhtala* actually teaches away from the presently claimed compounds and cannot be relied on to establish a *prima facie* case of obviousness.

Moreover, as Appellants have already discussed on the record, the Office has erred by combining *Karjalainen* and *Huhtala*. A *prima facie* case of obviousness cannot be established when the cited references teach away from one another. *See* M.P.E.P. § 2145. That is exactly the situation in the present case. *Karjalainen* teaches a class of compounds, which are generally "very selective alpha2 ***agonists***," whereas *Huhtala* discloses compounds generally "exhibiting alpha2-***antagonistic*** activity." *Karjalainen* at page 1, lines 8-9; *Huhtala* at page 14, first full paragraph. As discussed in Appellants'

January 30, 2008, Response at pages 7-8, the compounds of *Huhtala* necessarily require a bulky $(CR_2R_3)_r$-R_1 group–a feature that does not overlap with the compounds disclosed in *Karjalainen*. Absent that sterically cumbersome group, the compounds disclosed in *Karjalainen* have the opposite activity at the alpha2 adrenoreceptor, and as a result are used to treat different diseases and conditions. *Compare Karjalainen* at page 1, lines 8-14 to *Huhtala* at page 14, second full paragraph. In fact, compounds of *Huhtala*, i.e., antagonists, "may also be used for the **reversal** of the effects of alpha2-agonists," i.e., the compounds of *Karjalainen*. *Huhtala* at pages 13-14 (emphasis added). Therefore, not only does *Huhtala* fail to compensate for *Karjalainen's* deficiencies and teach away from the presently claimed esters, it also teaches away from its combination with *Karjalainen*. Therefore, for the reasons provided herein, Appellants respectfully request withdrawal of this rejection.

II. Rejection of claims 4, 8, and 10 under 35 U.S.C. § 103(a)

Appellants respectfully point out that the presently pending claims 4, 8, and 10 recite a compound according to claim 1 that is 4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1H-imidazol-1-ium chloride, i.e., where R is the 2,2-dimethyl propyl group (lower alkyl). Appellants assert that that compound and the corresponding method of treatment and pharmaceutical composition claims (e.g., presently pending claims 4, 8, and 10) are non-obvious over *Karjalainen* either alone or in combination with *Huhtala*. Specifically, the Office has failed to establish a *prima facie* case of obviousness with respect to claims 4, 8, and 10 for the reasons already present above, as well as the further arguments presented below.

Rejection over Karjalainen Alone

The Office asserts that "[t]he difference between the compounds of the prior art and the compounds instantly claimed is that the instant claimed compounds are generically described in the prior art." Final Office Action at 3. Appellants respectfully point out that the presently recited compound 4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1H-imidazol-1-ium chloride is not a member of the express genus of *Karjalainen* because R_6, R_7, and R_8 of *Karjalainen* are not specifically defined to include an ester group, let alone the presently claimed pivaloyl (a.k.a. 2,2-dimethylpropanoyloxy) group. *See Karjalainen* Abstract.

Similarly, the presently claimed compound is not expressly disclosed as a possible ester derivative of the *Karjalainen* compounds. Although, *Karjalainen* specifically contemplates that when one or more of R_4 to R_8 are hydroxy groups they may form "lower alkyl esters, such as the methyl, ethyl and propyl esters," (page 4, lines 27-28, assuming *Karjalainen* meant the situation where E above is methyl, ethyl, and propyl), the presently recited compound of claims 4, 8, and 10 possesses a 2,2-dimethylpropyl group and not a methyl, ethyl, or propyl group.

Moreover, not one of the specific compounds disclosed in *Karjalainen* on pages 13-39 includes ***any*** ester functional group, let alone in the 6-position of the indane ring as required by the present claims. In other words, even though *Karjalainen* generally teaches that its compounds may be derivatized as lower alkyl esters, none of the specific compounds disclosed includes such derivatization, even though some of those compounds, e.g., Compound 2 and Example 9, that include hydroxy groups in positions R_6, R_7, or R_8. As a result, the specific teaching of *Karjalainen* actually teaches away

from the presently claimed compounds. Therefore, for the reasons presented herein, this rejection should be withdrawn.

Rejection over Karjalainen and Huhtala

Similarly, claims 4, 8, and 10, are non-obvious over *Karjalainen* in view of *Huhtala* for the reasons above and because *Huhtala* does not specifically point out a pivaloyl group appended to any of the free hydroxyl groups of *Huhtala's* recited compounds. Therefore, because *Huhtala* provides no more guidance to one of skill in the art to modify the generic compounds of *Karjalainen* to arrive at the presently claimed compound of claims 4, 8, and 10, this rejection should be withdrawn.

Conclusion

For the reasons given above, reversal of the Office's rejection and the allowance pending claims 1-10 are respectfully requested.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17, which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

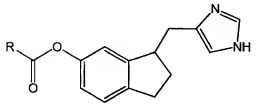
Dated: December 10, 2008

By: _____

Jill K. MacAlpine
Reg. No. 60,475
(202) 408-4000

Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii)

1. (Previously presented) A compound of general formula I,



(I)

or a pharmaceutically acceptable salt or hydrate thereof, wherein R represents unsubstituted or substituted lower alkyl, unsubstituted or substituted aryl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted lower alkylamino or a saturated five or six membered heterocyclic group containing one or two nitrogen atoms.

2. (Original) A compound according to claim 1, wherein R represents unsubstituted or substituted lower alkyl or unsubstituted or substituted aryl.

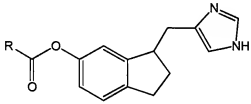
3. (Original) A compound according to claim 2, wherein R represents unsubstituted or substituted lower alkyl.

4. (Previously presented) A compound according to claim 3, said compound being 4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1H-imidazol-1-ium chloride.

5. (Previously presented) A compound according to claim 3, said compound being 4-(6-acetoxyindan-1-ylmethyl)-1H-imidazol-1-ium chloride.

6. (Previously presented) A compound according to claim 3, said compound being 4-(6-butyryloxyindan-1-ylmethyl)-1H-imidazol-1-ium chloride.

7. (Previously Presented) A method for the treatment of hypertension, glaucoma, migraine, diarrhea, ischemia, addiction to a chemical substance, hypotension, shock, cardiopulmonary resuscitation, a withdrawal syndrome, congestive heart failure, anxiety, or for achieving sedation or analgesia, or for reducing nasal congestion, or for achieving anesthesia with an adjunct, which comprises administering to a mammal in need thereof an effective amount of a compound of formula I,

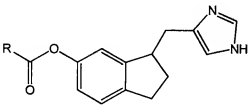


(I)

or a pharmaceutically acceptable salt or hydrate thereof, wherein R is as defined in claim 1.

8. (Previously presented) A method according to claim 7, wherein the compound is 4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1H-imidazol-1-ium chloride.

9. (Previously presented) A pharmaceutical composition which comprises as an active agent a compound of formula I,



(I)

or a pharmaceutically acceptable salt or hydrate thereof, wherein R is as defined in claim 1, and optionally a pharmaceutically acceptable excipient.

10. (Original) A pharmaceutical composition according to claim 9, wherein the compound is 4-[6-(2,2-dimethylpropanoyloxy)indan-1-ylmethyl]-1H-imidazol-1-ium chloride.

Claims 11-12. (Canceled).

Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)

None.

Related Proceedings Appendix to Appeal Brief Under Rule 41.37(c)(1)(x)

None.